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Septal Lesions as a Model for Evaluating Potential Cognition Enhancers

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14.1. Introduction

The loss of cholinergic input to the cortex and hippocampus is the most reliable neurotransmitter abnormality found in Alzheimer’s disease. Moreover, pharmacological disruption of cholinergic function impairs cognitive performance in experimental animals and humans. Thus, cholinergic dysfunction has been thought to play an important role in the cognitive deficits characteristic of Alzheimer’s disease. Given that hippocampal cholinergic input arises mainly from cholinergic neurons in the septal area (medial septum and diagonal band of Broca), a septal lesion model has been used extensively for preclinical evaluation of potential treatments for Alzheimer’s disease. In rodents, septal lesions impair performance in a variety of learning and memory tasks, and the ability of compounds to attenuate this deficit can be used as an index of cognition-enhancing potential. In this chapter, we will review some preclinical results with pharmacological agents and address the validity and utility of this model. Because nonselective lesion techniques have historically been used, we will also address issues that have arisen regarding the role of cholinergic dysfunction in the cognitive deficits produced by septal lesions. In addition, we will assess the impact of other behavioral effects of septal lesions, such as increased reactivity, on the use of this lesion to model impaired cognition.

Alzheimer’s disease (AD) is a neurodegenerative disorder estimated to afflict some 4 million people in the United States alone. The most obvious symptom of the disease is a progressive decline in cognitive function that eventually renders the patient incapable of living independently. Although a tentative diagnosis of AD can be made based on behavioral evaluation and by ruling out other potential causes of cognitive decline, it is not possible to diagnose AD definitively except by direct observation of brain histopathology. The hallmark of the disease is the presence of neurofibrillary tangles and senile plaques in the brain. The degree of histopathology has been reported to correlate well with the magnitude of cognitive impair-
ment (Blessed, Tomlinson, and Roth 1968; Wilcock and Esiri 1982), and the increased presence of these abnormalities in areas believed to be important for cognitive processing suggests that plaques and tangles may play a direct role in the disease process (Hardy and Allsop 1991; Simonian, Rebeck, and Hyman 1994).

Development of treatments for AD has been hampered by the lack of a generally accepted animal model. Mice that have been genetically altered to overexpress the major component of senile plaques, β-amyloid, have been produced (Games et al. 1995; Moran et al. 1995). These animals display some of the histopathological features of AD and cognitive impairment, but they have not been fully characterized and are not widely available. Moreover, it is not yet entirely certain that β-amyloid overproduction is the basis for the development of AD. Given the lack of a clear understanding of the disease process, many treatment strategies have focused on relieving symptoms, particularly the cognitive decline.

Although there is no animal model of AD per se, experimental animals have been used extensively in attempts to identify cognition-enhancing agents that might be useful in AD (for reviews, see Sarter, Hagan, and Dudchenko 1992a, b; Decker 1995; McDonald and Overmier 1998). In some cases, the cognitive effects of compounds given to normal animals have been used to identify potential cognition enhancers. This is based on the reasoning that compounds that improve cognitive function in normal animals may be likely to have general cognition-enhancing properties. It is more typical, however, that identification of potential cognitive enhancers has involved the use of an impairment model. Some impairment models make no attempt to parallel the neurobiology of AD, but the more common approach has been to mimic some aspect of the disease.

One approach to modeling the cognitive impairment of AD has been to disrupt hippocampal function. As noted earlier, it has been suggested that senile plaques are more prominent in brain areas important for cognitive processing. In particular, the primary input and output pathways of the hippocampal formation appear to be disrupted, leading to the characterization of AD as producing a “disconnection” of the hippocampus (Hyman et al. 1984). The hippocampus, of course, is believed to play a central role in learning and memory; and disruption of hippocampal inputs and outputs could be important in the etiology of cognitive deficits in AD. Major input pathways into the hippocampus arise from the entorhinal cortex and the septal area, and lesions of these areas have been used to model the cognitive impairments of AD (Kesner 1988; Myhrer 1993).

Lesions of the septal area have the added benefit of disrupting cholinergic input to the hippocampus, mimicking yet another significant feature of AD—cholinergic hypofunction. Declines in cholinergic innervation of the hippocampus and cortex were first noted more than 20 years ago using biochemical techniques (Bowen et al. 1976; Davies and Maloney 1976). This cholinergic deficit was subsequently ascribed to neuronal loss in the cholin-